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=> s sonic (n) hedgehog
L1 6720 SONIC (N) HEDGEHOG

=> s antisense or (anti (n) sense) or (complem? (2n) oligonucl? or nucl?)
L2 4746753 ANTISENSE OR (ANTI (N) SENSE) OR (COMPLEM? (2N) OLIGONUCL? OR
NUCL?)

=> s l1 and l2
L3 775 L1 AND L2

=> s antisense or (anti (n) sense) or (complem? (2n) (oligonucl? or nucl?))
L4 129741 ANTISENSE OR (ANTI (N) SENSE) OR (COMPLEM? (2N) (OLIGONUCL? OR
NUCL?))

=> s l4 and l3
L5 107 L4 AND L3

=> s l4 (5n) l3
PROXIMITY OPERATOR LEVEL NOT CONSISTENT WITH
FIELD CODE - 'AND' OPERATOR ASSUMED 'L19 (5A) L13'
PROXIMITY OPERATOR LEVEL NOT CONSISTENT WITH
FIELD CODE - 'AND' OPERATOR ASSUMED 'L20 (5A) L14'
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FIELD CODE - 'AND' OPERATOR ASSUMED 'L22 (5A) L16'
PROXIMITY OPERATOR LEVEL NOT CONSISTENT WITH
FIELD CODE - 'AND' OPERATOR ASSUMED 'L23 (5A) L17'
L6 107 L4 (5N) L3

=> d his

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FILE 'MEDLINE, BIOSIS, EMBASE, CA, SCISEARCH' ENTERED AT 23:33:36 ON 05
OCT 2003

L1 6720 S SONIC (N) HEDGEHOG
 L2 4746753 S ANTISENSE OR (ANTI (N) SENSE) OR (COMPLEM? (2N) OLIGONUCL? OR
 L3 775 S L1 AND L2
 L4 129741 S ANTISENSE OR (ANTI (N) SENSE) OR (COMPLEM? (2N) (OLIGONUCL? O
 L5 107 S L4 AND L3
 L6 107 S L4 (5N) L3

=> s l4 and l1
 L7 107 L4 AND L1

=> s l4 (s) l1
 L8 42 L4 (S) L1

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 L9 15 DUP REM L8 (27 DUPLICATES REMOVED)

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=> d l10 ibib abs

L10 ANSWER 1 OF 10 MEDLINE on STN
 ACCESSION NUMBER: 1998167903 MEDLINE
 DOCUMENT NUMBER: 98167903 PubMed ID: 9435297
 TITLE: Control of somite patterning by Sonic hedgehog and its downstream signal response genes.
 AUTHOR: Borycki A G; Mendham L; Emerson C P Jr
 CORPORATE SOURCE: Department of Cell and Developmental Biology, University of Pennsylvania School of Medicine, Philadelphia, PA 19104-6058, USA.
 CONTRACT NUMBER: HD-07796 (NICHD)
 SOURCE: DEVELOPMENT, (1998 Feb) 125 (4) 777-90.
 Journal code: 8701744. ISSN: 0950-1991
 PUB. COUNTRY: ENGLAND: United Kingdom
 DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
 LANGUAGE: English
 FILE SEGMENT: Priority Journals
 ENTRY MONTH: 199804
 ENTRY DATE: Entered STN: 19980410
 Last Updated on STN: 19980410
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AB In the avian embryo, previous work has demonstrated that the notochord provides inductive signals to activate myoD and pax1 regulatory genes, which are expressed in the dorsal and ventral somite cells that give rise to myotomal and sclerotomal lineages. Here, we present bead implantation and antisense inhibition experiments that show that **Sonic hedgehog** is both a sufficient and essential notochord signal molecule for myoD and pax1 activation in somites. Furthermore, we show that genes of the Sonic hedgehog signal response pathway, specifically patched, the Sonic hedgehog receptor, and gli and gli2/4, zinc-finger transcription factors, are activated in coordination with somite formation, establishing that Sonic hedgehog response genes play a regulatory role in coordinating the response of somites to the constitutive notochord Sonic hedgehog signal. Furthermore, the expression of patched, gli and gli2/4 is differentially patterned in the somite, providing mechanisms for differentially transducing the Sonic hedgehog signal to the myotomal and sclerotomal lineages. Finally, we show that the activation of gli2/4 is controlled by the process of somite formation and signals from the surface ectoderm, whereas upregulation of patched and activation of gli is controlled by the process of somite formation and a

Sonic hedgehog signal. The Sonic hedgehog signal response genes, therefore, have important functions in regulating the initiation of the Sonic hedgehog response in newly forming somites and in regulating the patterned expression of myoD and pax1 in the myotomal and sclerotomal lineages following somite formation.

=> d l10 ibib abs 2-10

L10 ANSWER 2 OF 10 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC. on STN
ACCESSION NUMBER: 2001:520914 BIOSIS
DOCUMENT NUMBER: PREV200100520914
TITLE: cGMP enhances the Sonic hedgehog response in neural plate cells.
AUTHOR(S): Robertson, Christie P.; Gibbs, Sarah M.; Roelink, Henk (1)
CORPORATE SOURCE: (1) Department of Biological Structure, Program in Neurobiology and Behavior, and Center for Developmental Biology, University of Washington, Seattle, WA, 98195: roelink@u.washington.edu USA
SOURCE: Developmental Biology, (October 1, 2001) Vol. 238, No. 1, pp. 157-167. print. ISSN: 0012-1606.
DOCUMENT TYPE: Article
LANGUAGE: English
SUMMARY LANGUAGE: English

AB The elaboration of distinct cell types during development is dependent on a small number of inductive molecules. Among these inducers is **Sonic hedgehog** (Shh), which, in combination with other factors, patterns the dorsoventral (DV) axis of the nervous system. The response of a cell is dependent in part on its **complement** of cyclic **nucleotides**. cAMP antagonizes Shh signaling, and we examined the influence of cGMP on the Shh response. Cells in chick neural plate explants respond to Shh by differentiating into ventral neural-cell types. Exposure of intermediate-zone explants to cGMP analogs enhanced their response to Shh in a dose-dependent manner. The Shh response was also enhanced in dorsal-zone explants exposed to chick natriuretic peptide (chNP), which stimulates cGMP production by membrane-bound guanylate cyclase (mGC). Addition of chNP to intermediate-zone explants did not enhance the Shh response, consistent with a reported lack of mGC in this region of the neural tube. Finally, the presence of a nitric oxide (NO)-sensitive guanylate cyclase (GC) was established by demonstrating cGMP immunoreactivity in neural tissue following NO stimulation of whole chick embryos. Intracellular levels of cGMP and cAMP may thus provide a mechanism through which other factors modulate the Shh response during neural development.

L10 ANSWER 3 OF 10 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC. on STN
ACCESSION NUMBER: 2001:516345 BIOSIS
DOCUMENT NUMBER: PREV200100516345
TITLE: Hedgehog signaling is required for primary motoneuron induction in zebrafish.
AUTHOR(S): Lewis, Katharine E.; Eisen, Judith S. (1)
CORPORATE SOURCE: (1) Institute of Neuroscience, 1254 University of Oregon, Eugene, OR, 97403: eisen@uoregon.edu USA
SOURCE: Development (Cambridge), (September, 2001) Vol. 128, No. 18, pp. 3485-3495. print. ISSN: 0950-1991.
DOCUMENT TYPE: Article
LANGUAGE: English
SUMMARY LANGUAGE: English

AB **Sonic hedgehog** (Shh) is crucial for motoneuron development in chick and mouse. However, zebrafish embryos homozygous for

a deletion of the *shh* locus have normal numbers of motoneurons, raising the possibility that zebrafish motoneurons may be specified differently. Unlike other vertebrates, zebrafish express three *hh* genes in the embryonic midline: *shh*, *echidna hedgehog* (*ehh*) and *tiggywinkle hedgehog* (*twhh*). Therefore, it is possible that *Twhh* and *Ehh* are sufficient for motoneuron formation in the absence of *Shh*. To test this hypothesis we have eliminated, or severely reduced, all three *Hh* signals using mutations that directly or indirectly reduce *Hh* signaling and **antisense** morpholinos. Our analysis shows that *Hh* signals are required for zebrafish motoneuron induction. However, each of the three zebrafish *Hhs* is individually dispensable for motoneuron development because the other two can compensate for its loss. Our results also suggest that *Twhh* and *Shh* are more important for motoneuron development than *Ehh*.

L10 ANSWER 4 OF 10 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC. on STN

ACCESSION NUMBER: 2001:492567 BIOSIS

DOCUMENT NUMBER: PREV200100492567

TITLE: The Alzheimer-related gene presenilin-1 facilitates sonic hedgehog expression in *Xenopus* primary neurogenesis.

AUTHOR(S): Paganelli, Alejandra R.; Ocana, Oscar H.; Prat, Maria I.; Franco, Paula G.; Lopez, Silvia L.; Morelli, Laura; Adamo, Ana M.; Riccomagno, Martin M.; Matsubara, Etsuro; Shoji, Mikio; Affranchino, Jose L.; Castano, Eduardo M.; Carrasco, Andres E. (1)

CORPORATE SOURCE: (1) Laboratorio de Embriologia Molecular, Facultad de Medicina, Instituto de Biologia Celular y Neurociencias, Universidad de Buenos Aires, Paraguay 2155, 3rd piso (1121), Buenos Aires: rqcarras@mail.retina.ar Argentina

SOURCE: Mechanisms of Development, (September, 2001) Vol. 107, No. 1-2, pp. 119-131. print.
ISSN: 0925-4773.

DOCUMENT TYPE: Article

LANGUAGE: English

SUMMARY LANGUAGE: English

AB We analyzed the influence of presenilins on the genetic cascades that control neuronal differentiation in *Xenopus* embryos. Resembling **sonic hedgehog** (*shh*) overexpression, presenilin mRNA injection reduced the number of N-tubulin+ primary neurons and modulated Gli3 and Zic2 according to their roles in activating and repressing primary neurogenesis, respectively. Presenilin increased *shh* expression within its normal domain, mainly in the floor plate, whereas an **antisense** X-presenilin- α morpholino oligonucleotide reduced *shh* expression. Both *shh* and presenilin promoted cell proliferation and apoptosis, but the effects of *shh* were widely distributed, while those resulting from presenilin injection coincided with the range of *shh* signaling. We suggest that presenilin may modulate primary neurogenesis, proliferation, and apoptosis in the neural plate, through the enhancement of *shh* signaling.

L10 ANSWER 5 OF 10 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC. on STN

ACCESSION NUMBER: 2001:196110 BIOSIS

DOCUMENT NUMBER: PREV200100196110

TITLE: The effects of 5-Aza-2'-deoxycytidine (d-AZA) on sonic hedgehog expression in mouse embryonic limb buds.

AUTHOR(S): Branch, Stacy (1); Smoak, Ida W.

CORPORATE SOURCE: (1) Department of Toxicology, North Carolina State University, Method Road, Unit 4, Raleigh, NC, 27695:
Stacy.Branch@ncsu.edu USA

SOURCE: Toxic Substance Mechanisms, (April June, 2000)
Vol. 19, No. 2, pp. 125-133. print.
ISSN: 1076-9188.

DOCUMENT TYPE: Article

LANGUAGE: English

SUMMARY LANGUAGE: English

AB 5-Aza-2'-deoxycytidine (d-AZA) causes temporally-related defects in the mouse. At 1.0 mg/kg on gestational day (GD) 10, d-AZA causes hindlimb phocomelia. **Sonic hedgehog** (Shh) plays a significant role in the normal development of limbs in rodent species. **Sonic hedgehog** peptides, found in the posterior mesenchyme of limb buds, are involved in patterning functions and in the regulation of both anterior-posterior polarity and proximal-distal outgrowth of the limb. The objective of the present study was to analyze alterations in Shh expression subsequent to d-AZA exposure. Pregnant mice were treated with d-AZA via intraperitoneal injection on GD 10. Controls were untreated. The reverse transcription-polymerase chain reaction (RT-PCR), whole mount in situ hybridization (ISH), and whole mount immunohistochemistry (WMI) were used to analyze expression patterns of Shh. For RT-PCR, embryonic hindlimb buds (buds) were taken 0, 4, 8, 12, or 24 hr after exposure. Cyclophilin was used as the baseline monitor. RNA was transcribed to cDNA and used as template with Shh specific primers for amplification. Whole embryos were collected 12 and 24 hr posttreatment for ISH. An **antisense** primer specific for Shh was used in an oligo-based ISH protocol. Whole embryos were collected 36 and 48 hr posttreatment for WMI. The antibody corresponding to the amino terminal subunit of the Shh peptide was used. There was a treatment related up-regulation of Shh transcripts by 12 and 24 hr posttreatment. The protein response of up-regulation was detectable by 36 and 48 hr posttreatment. Our data suggest that 5-aza-2'-deoxycytidine-induced hindlimb defects may be associated with alterations in the level of Shh expression. This may be part of a cascade of signaling events involved in d-AZA-induced hindlimb defects. Work is ongoing to determine the relationship of other gene species that may cooperate with Shh in the induction of the hindlimb defects.

L10 ANSWER 6 OF 10 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC. on STN

ACCESSION NUMBER: 2001:107632 BIOSIS

DOCUMENT NUMBER: PREV200100107632

TITLE: Bone anabolic effects of Sonic/Indian hedgehog are mediated by BMP-2/4-dependent pathways in the neonatal rat metatarsal model.

AUTHOR(S): Krishnan, Venkatesh (1); Ma, Yanfei L.; Moseley, Jane M.; Geiser, Andrew G.; Friant, Sylvie; Frolik, Charles A.

CORPORATE SOURCE: (1) Endocrinology Division, Lilly Corporate Center, Eli Lilly and Co., Indianapolis, IN, 46285: Krishnan_Gary@lilly.com USA

SOURCE: Endocrinology, (February, 2001) Vol. 142, No. 2, pp. 940-947. print. ISSN: 0013-7227.

DOCUMENT TYPE: Article

LANGUAGE: English

SUMMARY LANGUAGE: English

AB A neonatal rat metatarsal organ culture model has been employed to study the anabolic effects of Sonic/Indian hedgehog and BMP-4. In this culture system, a significant increase in endochondral ossification is measured by an increase in length of mineralized bone, after daily treatment for 7 days with **Sonic hedgehog** protein (Shh-N). Previous evidence indicated that PTH related protein (PTHrP) is a critical target of hedgehog function in endochondral ossification. Using a PTHrP blocking antibody, it is shown that hedgehog mediates this activity via pathways other than through PTHrP. A dose-related increase in endochondral ossification is observed when metatarsals are treated with 25 ng/ml recombinant human bone morphogenetic protein 4 (BMP-4). However, this activity is not evident at higher doses of BMP-4 (200 ng/ml). High doses of BMP-4 resulted in increased expression of noggin messenger RNA and cotreatment of noggin and Shh-N resulted in reversal of the anabolic

action of Shh-N. This observation suggests that BMP-4 signaling can influence the Shh-N mediated increase in endochondral ossification. Finally, we show that the Shh-N and BMP-4 mediated increase in endochondral ossification is reversed by treatment with **antisense** oligonucleotides targeted against Cbfa1. Thus, this report identifies Shh-N as an inducer of endochondral ossification that mediates its effect via BMP-4 and Cbfa1-dependent pathways.

L10 ANSWER 7 OF 10 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC. on STN
ACCESSION NUMBER: 2000:503825 BIOSIS
DOCUMENT NUMBER: PREV200000503825
TITLE: Effective targeted gene 'knockdown' in zebrafish.
AUTHOR(S): Nasevicius, Aidan; Ekker, Stephen C. (1)
CORPORATE SOURCE: (1) Department of Genetics, Cell Biology and Development,
Arnold and Mabel Beckman Center for Transposon Research at
the University of Minnesota, Minneapolis, MN USA
SOURCE: Nature Genetics, (October, 2000) Vol. 26, No. 2,
pp. 216-220. print.
ISSN: 1061-4036.

DOCUMENT TYPE: Article
LANGUAGE: English
SUMMARY LANGUAGE: English

AB The sequencing of the zebrafish genome should be completed by the end of 2002. Direct assignment of function on the basis of this information would be facilitated by the development of a rapid, targeted 'knockdown' technology in this model vertebrate. We show here that **antisense**, morpholino-modified oligonucleotides (morpholinos) are effective and specific translational inhibitors in zebrafish. We generated phenocopies of mutations of the genes no tail, chordin, one-eyed-pinhead, nacre and sparse, removing gene function from maternal through post-segmentation and organogenesis developmental stages. We blocked expression from a ubiquitous green fluorescent protein (GFP) transgene, showing that, unlike tissue-restricted limitations found with RNA-based interference in the nematode, all zebrafish cells readily respond to this technique. We also developed also morpholino-based zebrafish models of human disease. Morpholinos targeted to the uroporphyrinogen decarboxylase gene result in embryos with hepatoerythropoietic prophyria. We also used morpholinos for the determination of new gene functions. We showed that embryos with reduced **sonic hedgehog** signalling and reduced tiggly-winkle hedgehog function exhibit partial cyclopia and other specific midline abnormalities, providing a zebrafish genetic model for the common human disorder holoprosencephaly. Conserved vertebrate processes and diseases are now amenable to a systematic, in vivo, reverse-genetic paradigm using zebrafish embryos.

L10 ANSWER 8 OF 10 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC. on STN
ACCESSION NUMBER: 2000:255457 BIOSIS
DOCUMENT NUMBER: PREV200000255457
TITLE: Function for hedgehog genes in zebrafish retinal development.
AUTHOR(S): Stenkamp, Deborah L. (1); Frey, Ruth A.; Prabhudesai, Shubhangi N.; Raymond, Pamela A.
CORPORATE SOURCE: (1) Department of Biological Sciences, University of Idaho, Moscow, ID, 83844-3051 USA
SOURCE: Developmental Biology, (April 15, 2000) Vol. 220, No. 2, pp. 238-252. print..
ISSN: 0012-1606.

DOCUMENT TYPE: Article
LANGUAGE: English
SUMMARY LANGUAGE: English

AB The hedgehog (hh) genes encode secreted signaling proteins that have important developmental functions in vertebrates and invertebrates. In

Drosophila, expression of hh coordinates retinal development by propagating a wave of photoreceptor differentiation across the eye primordium. Here we report that two vertebrate hh genes, **sonic hedgehog** (shh) and **tiggy-winkle hedgehog** (twhh), may perform similar functions in the developing zebrafish. Both shh and twhh are expressed in the embryonic zebrafish retinal pigmented epithelium (RPE), initially in a discrete ventral patch which then expands outward in advance of an expanding wave of photoreceptor recruitment in the subjacent neural retina. A gene encoding a receptor for the hedgehog protein, ptc-2, is expressed by retinal neuroepithelial cells. Injection of a cocktail of **antisense** (alphashh/alphatwhh) oligonucleotides reduces expression of both hh genes in the RPE and slows or arrests the progression of rod and cone photoreceptor differentiation. Zebrafish strains known to have mutations in Hh signaling pathway genes similarly exhibit retardation of photoreceptor differentiation. We propose that hedgehog genes may play a role in propagating photoreceptor differentiation across the developing eye of the zebrafish.

L10 ANSWER 9 OF 10 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC. on STN
 ACCESSION NUMBER: 2000:3975 BIOSIS
 DOCUMENT NUMBER: PREV200000003975
 TITLE: Flik, a chick follistatin-related gene, functions in gastrular dorsalisation/neural induction and in subsequent maintenance of midline Sonic hedgehog signalling.
 AUTHOR(S): Towers, Paula; Patel, Ketan; Withington, Sarah; Isaac, Alison; Cooke, Jonathan (1)
 CORPORATE SOURCE: (1) Division of Developmental Neurobiology, National Institute for Medical Research, The Ridgeway, Mill Hill, London, NW7 1AA UK
 SOURCE: Developmental Biology, (Oct. 15, 1999) Vol. 214, No. 2, pp. 298-317.
 ISSN: 0012-1606.
 DOCUMENT TYPE: Article
 LANGUAGE: English
 SUMMARY LANGUAGE: English

AB We have targetted the chick gene Flik with **antisense** oligodeoxynucleotide treatment at gastrular stages, when it is expressed in organiser-derived structures of the midline (K. Patel et al., 1996, Dev. Biol. 178, 327-342). A specific syndrome of deficient axial patterning and holoprosencephaly is produced. Most aspects of this syndrome can be understood as due to attenuation of dorsalisating and neural-inducing signals during gastrulation, followed by failure to maintain the later signals from chordamesoderm/neural midline that pattern the mesodermal and neural cross sections during subsequent stages. Anatomical effects are first apparent at early neurula stages and correspond with what might be expected from a reduced counteraction of the ventralising Bone morphogenetic protein (BMP) pathway at the earlier stages, coupled with inadequate **Sonic hedgehog** (Shh) signaling subsequently. Delay in the clearing of BMP-4 RNA expression from the presumptive neural region at gastrulation is indeed seen, though chordin RNA expression within organiser derivatives remains normal. Subsequently, specific attenuation of chordamesoderm and neural midline Shh expression is observed. Brief preincubation of stage 4 chick blastoderms in supernatant from Xenopus oocytes that have been injected with Flik RNA prolongs and enhances the competence of their peripheral epiblast to respond to neural inductive signals from grafted Hensen's nodes. This effect specifically mimics that recently observed using mug/ml solutions of recombinant Follistatin (D. J. Connolly et al., 1999, Int. J. Dev. Biol., in press), further suggesting that Flik protein might act in vivo by somehow modulating activity of signalling pathways through BMP or other TGFbeta-related ligands. We discuss the significance of the observations in relation to recent ideas about neural induction, about

possible redundancy in gene action, and about subsequent patterning of the axial cross section, suggesting that aFlik function in autocrine/paracrine maintenance of later midline Shh signalling represents a role of the gene separate from that in primary dorsalisation/neural induction.

L10 ANSWER 10 OF 10 CA COPYRIGHT 2003 ACS on STN

ACCESSION NUMBER: 126:247273 CA

TITLE: Mouse whole embryo culture and antisense oligodeoxynucleotides: new approaches to studying genes involved in early development

AUTHOR(S): Sadler, Tom W.; Denno, Kelly M.; Potts, Linda Foerst
CORPORATE SOURCE: Department of Cell Biology and Anatomy, University of North Carolina at Chapel Hill, Chapel Hill, NC, 27599-7090, USA

SOURCE: Methods in Developmental Toxicology and Biology, [International Symposium on "Methods in Developmental Toxicology and Biology"], Berlin, May 31-June 2, 1995 (1997), Meeting Date 1995, 125-133. Editor(s): Klug, Stephan; Thiel, Renate. Blackwell: Oxford, UK.
CODEN: 64EWAK

DOCUMENT TYPE: Conference

LANGUAGE: English

AB **Antisense** oligodeoxynucleotides specific to genes Shh (**sonic hedgehog**), HNF-3.beta. (encoding hepatocyte nuclear factor 3.beta.), and Msx-1 were injected into mouse embryos at about 3-5 somite stage. Msx-1 antisense oligodeoxynucleotides induced defects in the craniofacial region. Antisense oligodeoxynucleotides to genes HNF-3.beta. and Shh induced cranial neural tube defects (exencephaly), kinking of the spinal cord, irregular somite formation, and caudal dysgenesis.